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Original Article

Effect of autologous platelet-rich plasma combined with sodium hyaluronate on clinical efficacy and serum inflammatory factors in patients with knee osteoarthritis

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Abstract: Objective: To observe the effect of autologous platelet-rich plasma combined with sodium hyaluronate on clinical efficacy and serum inflammatory factor levels in patients with knee osteoarthritis. Methods: A retrospective study was conducted on a total of 99 knee osteoarthritis patients who underwent arthroscopic surgery after failed conservative treatment in No. 215 Hospital of Shaanxi Nuclear Industry from January 2019 to January 2022. Among them, 45 patients treated with only sodium hyaluronate injection after arthroscopic debridement were grouped as the control group (CG), and 54 patients treated with platelet-rich plasma combined with intra-articular injection of sodium hyaluronate after arthroscopic debridement were the observation group (OG). Visual analogue scale/score (VAS) and Lysholm knee scale (LKS) were used to evaluate the clinical therapeutic effect before and 5 weeks after treatment, and ELISA was to detect the changes of matrix metalloproteinase-3 (MMP-3), interleukin-1β (IL-1β), high-sensitivity C-reactive protein (hs-CRP) and tumor necrosis factor-α (TNF-α) levels in the serum of patients before and 5 weeks after treatment. Risk factors affecting patient outcomes were analyzed by logistic regression. Results: Compared to theCG, the improvement of clinical efficacy in the OG was higher ($P < 0.05$), as well as its LKS score, while the VAS score after treatment in OG was markedly lower ($P < 0.05$). After treatment, MMP-3, IL-1β, hs-CRP, and TNF-α in the OG were significantly lower than those in the CG ($P < 0.05$). There was nodifference in the incidence rate of adverse reactions between the two groups ($P > 0.05$). Logistic regression analysis showed that younger age and lower BMI were protective factors for efficacy in the patients, while higher LKS and TNF-α were risk factors affecting the efficacy in the patients. Conclusion: Intra-articular injection of platelet-rich plasma combined with sodium hyaluronate in the treatment of knee osteoarthritis can significantly reduce the symptoms of knee joint pain, improving knee joint function and in vivo inflammatory response.

Keywords: Autologous platelet-rich plasma, sodium hyaluronate, knee osteoarthritis, clinical efficacy, serum inflammatory factors

Introduction

Osteoarthritis is the most common joint disease, usually characterized by slow progression, involving articular cartilage, subchondral bone, ligaments, synovium, and adjacent muscles [1]. It has been found that osteoarthritis patients with large joints have a relatively poor prognosis, which can result in disability at a later stage, placing a heavy burden on society [2]. Knee osteoarthritis is a common osteoarthritis in orthopedics, which is a cartilage destruction of the articular surface of the knee joint caused by cartilage degeneration, necrosis and shedding [3]. Patients have excessive mechanical loads acting on normal articular cartilage, or normal mechanical loads acting on damaged articular cartilage, which leads to the development of osteoarthritis [4]. Knee osteoarthritis has a long disease course and cannot be cured completely. The expenditure of medical costs and patients' inability to earn moneyor relatively reduced work intensity burdens both the family and patients financially [5]. In the United

States, the incidence of knee osteoarthritis is second only to cardiovascular disease among people over 50, with an incidence of 30-50% in people over 65 years of age [6]. With the improvement of medicine, the life expectancy of people continues to grow, and the incidence rate is on a gradually increasing trend. In addition, due to the high population base, the aging of the population in China is becoming serious, resulting in a large number of patients with knee osteoarthritis, bringing a huge economic burden and nursing costs to each patient's family and society [7].

There are currently many treatment options for knee osteoarthritis, which can be broadly divided into surgical and non-surgical treatments [8]. Both surgical and non-surgical treatment have achieved clinical results. However, there is still a lack of particularly simple, practical and effective treatment for the disease because the etiology and pathogenesis of knee osteoarthritis are not fully understood, and an ideal situation has not yet been achieved in terms of the effect or the process of treatment [9]. Sodium hyaluronate is the main component of synovial fluid, an ideal drug for the treatment of osteoarthritis, which can increase the lubrication function of joints and protect articular cartilage [10, 11]. A growing number of studies have revealed that platelet-rich plasma (PRP) has a good effect in the treatment of inflammatory diseases [12]. PRP contains a variety of growth factors that facilitate the repair of knee cartilage, and PRP treatment of knee osteoarthritis by intra-articular injection repairs cartilage defects and restores knee joint motor function [13]. PRP is a high concentration of platelet concentrate obtained by centrifugation and separation of autologous whole blood, with a relatively normal platelet concentration of 200,000/ul, and the platelet count in PRP after centrifugation can exceed 2 million/μl [14]. Moreover, PRP contains a large number of growth factors, mainly platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), fibroblast growth factor (FGF) and insulin-like growth factor (IGF), which promote chondrocyte proliferation, inhibit osteoclast function, induce the synthesis of cartilage matrix, and promote the healing of cartilage and other tissues [15, 16]. However, there is no systematic report on the therapeutic effect of combined treatment of autologous platelet-rich plasma and sodium hyaluronate in patients with knee osteoarthritis.

In this study, we aimed to analyze the effect of autologous platelet-rich plasma combined with sodium hyaluronate on the clinical efficacy and serum inflammatory factor levels in patients with knee osteoarthritis, to provide a reference for the feasibility of clinical treatment.

Materials and methods

Clinical information

A retrospective study was conducted on a total of 99 patients with knee osteoarthritis who underwent arthroscopic surgery after failure of conservative treatment in No. 215 Hospital of Shaanxi Nuclear Industry from January 2019 to January 2022. Among them, 45 patients treated with only sodium hyaluronate injection after arthroscopic debridement were grouped as the control group (CG), and 54 patients treated with platelet-rich plasma combined with intra-articular injection of sodium hyaluronate after arthroscopic debridement were set as the observation group (OG). This study was approved by the Medical Ethics Committee of No. 215 Hospital of Shaanxi Nuclear Industry.

Inclusion and exclusion criteria

Inclusion criteria: In line with the diagnostic criteria for knee osteoarthritis in the "Guidelines for the Diagnosis and Treatment of Osteoarthritis" [17]; Patients with failed conservative treatment; Patients diagnosed with Kellgren-Lawrence grades I-III; Patients with complete clinical data.

Exclusion criteria: Patients with knee joint tuberculosis, suppuration or intra-articular fracture; Patients with severe heart, lung, liver, kidney and other complications; Patients with psychosis, mental disorders and depression and unwilling or unable to cooperate with the experiment; Pregnant or breastfeeding patients; Intolerant to this treatment regimen.

Treatment regimen

The CG was treated with sodium hyaluronate (Shanghai Haohai Biotechnology Co., Ltd., GYZZ H20000326). Usage and dosage: sodium hyaluronate 2 mL/time after routine disinfection of the knee joint, once a week, was injected into the synovial fluid by withdrawing the lower edge of the patella and the lateral patellar ligament for 5 weeks.

The OG was treated with PRP on the basis of CG. The preparation method of PRP was as follows: 10 mL peripheral venous blood was collected and centrifuged in a high-speed rotary centrifuge at a rate of 1100 r/min for 8 min. A few red blood cells were collected from the supernatant and junction, and then centrifuged at 1100 r/min for 8 min. The upper anemic platelet plasma was removed to obtain PRP, which was then activated by adding 0.2 mL of 10% calcium chloride. After routine disinfection of the knee joint, PRP 2 mL/time, once a week, could be injected into the joint fluid by withdrawing the synovial fluid with the lower edge of the patella and the lateral patellar ligament as the puncture points for 5 weeks.

Serologic markers

Enzyme linked immunosorbent assay (ELISA) was used to detect changes in serum levels of matrix metalloproteinase-3 (MMP-3, ml026-254), interleukin-1β (IL-1β, ml058034), high-sensitivity C-reactive protein (hs-CRP, ml092-638) and tumor necrosis factor-α (TNF-α, ml077385) during treatment. The kit was purchased from Shanghai Enzyme Linked Immunology Co., Ltd.

Outcome measures

Main outcome measures: The clinical efficacy was compared between the two groups. Visual analogue scale/score (VAS) for pain [18] and Lysholm knee scale (LKS) [19] were used to evaluate the pain and knee ability function after treatment before and 5 weeks after treatment.

Secondary outcome measures: Clinical data of the two groups was compared. ELISA was used to detect the changes of matrix metalloproteinase-3 (MMP-3), interleukin-1β (IL-1β), high-sensitivity C-reactive protein (hs-CRP) and tumor necrosis factor-α (TNF-α) levels in serum of patients before surgery and 5 weeks after treatment. The incidence of adverse reactions during treatment was compared between the two groups. Risk factors affecting patient outcomes were analyzed with logistics regression.

Criteria for response assessment

Significantly effective: the clinical symptoms basically disappeared, the knee joint function recovered with no joint effusion or swelling, and the Lysholm score difference before and after treatment was ≥ 30 points. Effective: clinical symptoms and knee joint function improved, there was a small amount of joint effusion or slight swelling, with Lysholm score difference before and after treatment of 6 to 29 points. Invalid: the above criteria were not met. Clinical response rate = (markedly effective + effective)/total number 100%.

Statistical analysis

Data collected were analyzed using SPSS 20.0 (SPSS Inc., Chicago, IL, USA), and visualized using GraphPad Prism 8. Kolmogorov-Smirnov test was used to assess distribution normality. Data in this study conformed to a normal distribution, thus were presented as mean ± standard deviation, and were analyzed by t-test; specifically, Student t-test and Paired t-test were used for inter-group and intra-group comparison, respectively. Chi-square test was used to compare categorical variables, Logistics test was to analyze the risk factors affecting patients' efficacy, and receiver operating curve was to analyze the value of risk factors in predicting the efficacy of patients. $P < 0.05$ indicated statistical significance.

Results

Clinical information

The two cohorts of patients were comparable with no significant differences in terms of sex, age, BMI, course of disease, history of diabetes and history of hypertension ($P > 0.05$) (**Table 1**).

Comparison of efficacy evaluation

After treatment, the improvement of clinical efficacy in the OG was significantly better than that in the CG ($P < 0.05$, **Table 2**).

Changes in LKS and VAS scores before and after treatment

After treatment, LKS score was increased, while VAS score was decreased in both groups (both $P < 0.05$). Further comparison suggested that the OG held a higher LKS score than the CG after treatment, while its VAS score went markedly lower than that of the CG (both $P < 0.05$, **Figure 1**).

Table 1. Comparative analysis of baseline data

Variable	Control Group (n=45)	Observation Group (n=54)	x^2 Value	*P* Value
Gender			0.312	0.576
Male	25	33		
Female	20	21		
Age			0.303	0.581
≥ 55 years	25	27		
< 55 years	20	27		
BMI			0.325	0.568
≥ 23 kg/m^2	14	14		
< 23 kg/m^2	31	40		
Course of Disease			0.001	0.968
≥ 5 years	31	37		
< 5 years	14	17		
History of Diabetes			0.358	0.549
Yes	15	15		
No	30	39		
History of Hypertension			0.005	0.940
Yes	18	22		
No	27	32		

Note: Body Mass Index (BMI).

Changes of inflammatory factors before and after treatment

Comparing the changes of inflammatory factors before and after treatment between the two groups, it was found that MMP-3, IL-1β, hs-CRP and TNF-α in both groups decreased markedly compared with those before treatment (all P < 0.05). Further comparison showed that above indicators in the OG were much lower than those in the CG after treatment (all P < 0.05, **Figure 2**).

Adverse reactions comparison

Comparison of adverse reactions between the two groups showed no statistical difference in the incidence rate of adverse reactions (P > 0.05, **Table 3**).

Analysis of risk factors affecting the efficacy of patients

According to the clinical efficacy of the patients after treatment, there were 82 patients assigned into the effective group and 17 patients into the ineffective group. By univariate analysis, it was found that age, BMI, LKS score, IL-1β, and TNF-α were associated with patient treatment outcome (**Table 4**, P < 0.05). Subsequently, based on assigning values (**Table 5**), we conducted logistic regression analysis and found that younger age and lower BMI were protective factors for the efficacy of patients, while higher LKS and TNF-α were risk factors (**Table 6**, P < 0.05).

Discussion

Osteoarthritis is a disease caused by degenerative changes in the bone and joint, such as the hip, knee, shoulder, and elbow, with an incidence of 3% [20]. Among these, knee osteoarthritis accounts for the highest incidence of 60.1% in people over 60 [4]. Severe cases of knee osteoarthritis will develop into limited mobility, which seriously affects patients' life and health [6]. Therefore, how to take reasonable and effective treatment measures is of great significance to improve the life quality of knee osteoarthritis patients.

Sodium hyaluronate can improve the elasticity of knee joint fluid, make it difficult to damage, reduce the friction of articular cartilage, and protect the soft tissue in the knee joint [21]. Moreover, other studies [22] have found that intra-articular injection of sodium hyaluronate into the knee joint has a low and mild incidence of adverse reactions, which is suitable for non-steroidal anti-inflammatory drugs and analgesics when the effect is not significant, and has a better health and economic benefit for the early and mid-term treatment of knee osteoarthritis; so, intra-articular injection of sodium hyaluronate has also become a common means for the treatment of knee osteoarthritis. However, it can only relieve pain, and the duration of action is relatively short, so the therapeutic effect is often poor.

In recent years, many studies have reported that a variety of growth factors contained in platelet-rich plasma (PRP) are conducive to the repair of knee cartilage, and platelet-rich plasma (PRP) injection into the articular cavity is often chosen to repair cartilage defects and restore knee joint function of knee osteoarthritis patients [23]. However, in a study by Dório et

Table 2. Comparison of efficacy evaluation between the two groups

Grouping	Significantly effective	Effective	Invalid	Overall response rate
Control Group (n=45)	17 (37.78%)	15 (33.33%)	13 (28.89%)	32 (71.11%)
Observation Group (n=54)	27 (50.00%)	23 (42.59%)	4 (7.41%)	50 (92.59%)
x^2 value				7.964
P value				0.005

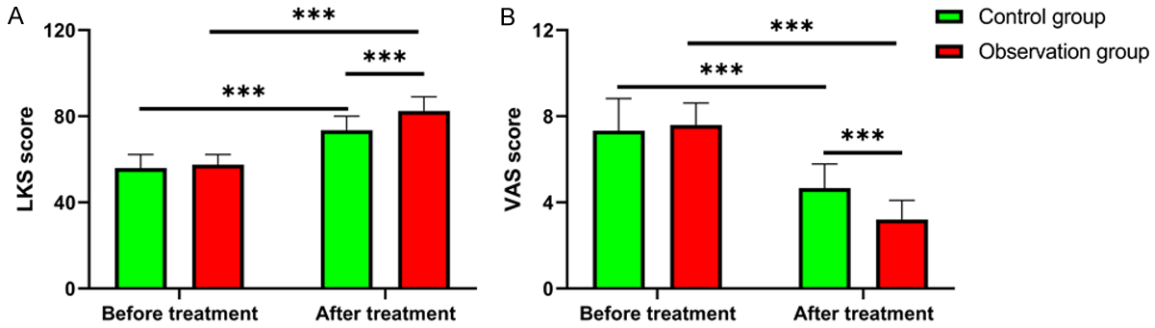

Figure 1. Changes of LKS and VAS scores before and after treatment in patients. A. Comparison of LKS score changes before and after treatment. B. Comparison of VAS score changes before and after treatment. Note: Visual analogue scale/score (VAS), Lysholm knee scale (LKS), * indicates P < 0.001.

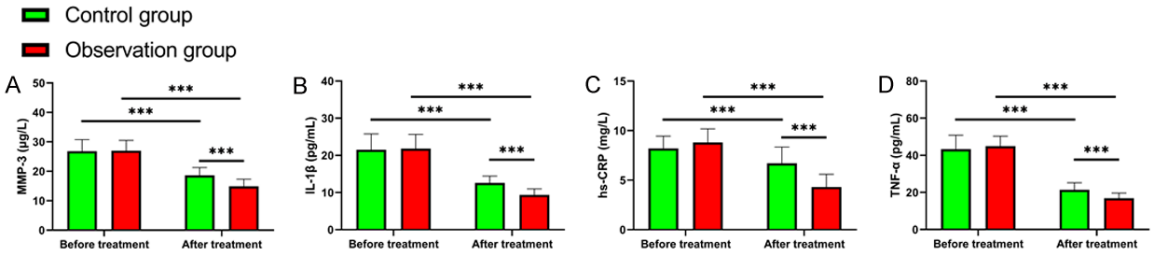

Figure 2. Changes of inflammatory factors before and after treatment. A. Comparison of MMP-3 changes before and after treatment. B. Comparison of IL-1β changes before and after treatment. C. Comparison of hs-CRP changes before and after treatment. D. Comparison of TNF-α changes before and after treatment. Note: Matrix metalloproteinase-3 (MMP-3), interleukin-1 (IL-1β), high-sensitivity C-reactive protein (hs-CRP) and tumor necrosis factor-α (TNF-α), P < 0.001.

Table 3. Comparison of Adverse Reactions between the two groups

Grouping	Hemarthrosis	Knee infection	Fever	Deep vein thrombosis	Total Occurrence
Control Group (n=45)	2 (4.44%)	3 (6.67%)	2 (4.44%)	1 (2.22%)	8 (17.77%)
Observation Group (n=54)	1 (1.85%)	2 (3.70%)	1 (1.85%)	1 (1.85%)	5 (9.25%)
x^2 value					1.561
P value					0.211

al. [24], patients with knee osteoarthritis were found not to be superior to placebo in terms of pain and functional improvement after PRP treatment. Minor transient increases in pain were more frequent in the PRP group. Moreover, in a study by Di et al. [25], although both sodium hyaluronate and PRP alone were effective in improving knee functional status and clinical symptoms, PRP did not provide an overall better clinical improvement than sodium hyaluronate in terms of symptom function improvement or duration of effect at different follow-up points. These studies suggested that both agents were equally effective as monotherapy

Table 4. Univariate analysis of factors affecting the treatment efficacy

Variable	Effective Group (n=82)	Invalid Group (n=17)	x^2 value	*P* value
Gender			0.316	0.573
Male (n=58)	47	11		
Female (n=41)	35	6		
Age			7.323	0.006
≥ 55 years old (n=52)	38	14		
< 55 years old (n=47)	44	3		
BMI			13.420	< 0.001
≥ 23 kg/m^2 (n=28)	17	11		
< 23 kg/m^2 (n=71)	65	6		
Course of Disease			0.034	0.852
≥ 5 years (n=68)	56	12		
< 5 years (n=31)	26	5		
History of Diabetes			1.149	0.283
Yes (n=30)	23	7		
No (n=69)	59	10		
History of Hypertension			2.892	0.089
Yes (n=40)	30	10		
No (n=59)	52	7		
LKS Score	56.17±5.52	60.00±4.58	2.669	0.008
VAS Score	7.46±1.21	7.52±1.50	0.194	0.845
MMP-3	26.59±3.63	28.36±3.32	1.856	0.065
IL-1β	21.28±4.04	23.59±3.43	2.199	0.030
hs-CRP	8.42±1.33	9.10±1.26	1.926	0.057
TNF-α	43.53±6.46	47.30±5.99	2.234	0.027

Note: Body Mass Index (BMI), Visual analogue scale/score (VAS), Lysholm knee scale (LKS), Matrix metalloproteinase-3 (MMP-3), interleukin-1 (IL-1β), high-sensitivity C-reactive protein (hs-CRP) and tumor necrosis factor-α (TNF-α).

Table 5. Assignment

Variable	Assignment
Age	≥ 55 years old =1, < 55 years old =0
BMI	≥ 23 kg/m^2 =1, < 23 kg/m^2 =0
LKS	Raw data used as continuous variables
IL-1β	Raw data used as continuous variables
TNF-α	Raw data used as continuous variables

Note: Body Mass Index (BMI), Lysholm knee scale (LKS), interleukin-1 (IL-1β).

and that PRP monotherapy was inferior to sodium hyaluronate in terms of pain relief. However, it remains unclear whether the combination of the two can function more effectively. In this study, we found that the overall clinical response rate in the observation group, or OG washigher than that in the control group, or CG, and LKS and VAS scores of patients were improved after treatment, without increasing the occurrence of adverse reactions in the patients. This suggests that sodium hyaluronate combined with PRP can effectively improve the therapeutic effect of knee osteoarthritis. The reason is that sodium hyaluronate is a branched-chain polyanionic polymer, which can effectively protect a variety of soft tissues in the knee joint cavity, and at the same time, it can provide nutrition for its metabolic activities, thereby relieving clinical symptoms such as knee joint swelling and morning stiffness and improving knee joint function [26]. PRP is platelet plasma rich in a variety of growth factors obtained from the patient's own venous blood after centrifugation, which can effectively improve cartilage matrix production function and promote chondrocyte production [27]. The combined use of the two promotes the recovery of a variety of soft tissues in the joint cavity, improves the knee stability, and plays a role in improving knee joint function and relieving pain.

At present, the new view stated that inflammation also plays an important role in the early stage of knee osteoarthritis lesions, and inflammatory cytokines affect the production of cytokines and enzymes through intracellular signal transduction pathways, thereby aggravating the progression of the disease [28]. MMP-3 is a cytokine involved in the pathogenesis of knee osteoarthritis and is closely related to cartilage matrix degradation in the knee joint, which can be reduced by inhibiting MMP-3 activity [29]. Many studies have revealed that the expression of TNF-α, IL-1, and hs-CRP in synovial fluid of OA patients is abnormally increased, resulting in cartilage progenitor cell disorder and chondrocyte death, accelerating joint aging and destruction. In addition, IL-1 can stimulate the production of reactive oxygen

Table 6. Multivariate analysis of factors affecting the treatment efficacy

Variable	B	S.E.	Wals	Sig.	Exp (B)	95% C.I. of EXP (B)	
						Lower limit	Upper limit
Age	-2.388	0.863	7.663	0.006	0.092	0.017	0.498
BMI	-1.480	0.696	4.524	0.033	0.228	0.058	0.890
LKS	0.161	0.078	4.256	0.039	1.174	1.008	1.368
IL-1β	0.158	0.082	3.667	0.055	1.171	0.996	1.377
TNF-α	0.136	0.060	5.058	0.025	1.145	1.018	1.289

Note: Body Mass Index (BMI), Lysholm knee scale (LKS), interleukin-1 (IL-1β).

species, and the generated free radicals can directly damage articular cartilage [30]. In our study, the levels of MMP-3, IL-1β, hs-CRP, and TNF-α in OG were markedly lower than those in CG after treatment, which indicated that the combined treatment had better inhibitory effect on the occurrence of inflammatory reactions in patients. This is mainly due to the fact that platelets in PRP are also a source of modulators of inflammatory mediators, and PRP is precisely able to affect tissue regulation by increasing growth factors in platelet levels and regulating the release of inflammatory factors, thereby reducing pain associated with knee osteoarthritis [31].

At the end of the study, we analyzed the risk factors affecting the efficacy of patients. Younger age and lower BMI were protective factors for patient efficacy, while higher LKS and TNF-α were risk factors affecting patient efficacy. From the pathophysiology of osteoarthritis, it is revealed that it is a process of articular surface hyaline cartilage degeneration with exposed and sclerotic subchondral bone, while with the increase of age, the hyaline cartilage regeneration ability of patients is poor, and the autologous recovery ability is slower than that of young people. This leads to unsatisfactory therapeutic results in patients [32]. While articular cartilage in patients with larger BMI is under high pressure, increased limited proliferation and destruction of chondrocytes is high which is the main reason for unsatisfactory outcomes [33]. In addition, overweight patients have more rapid osteophyte hyperplasia at the cartilage margin which is more painful than in non-overweight individuals [34]. However, patients with lower LKS have more notable limitation of their own knee joint function, which is bound to increase the difficulty of treatment [35]. Inflammation has been shown to play an essential role in the pathogenesis, and inflammatory cytokines secreted in patients who develop knee osteoarthritis are involved in the aggravation of inflammation, and patients with higher levels of inflammatory factors before treatment were found to be not conducive to treatment [36]. Therefore, providing targeted treatment according to the patient's own condition before treatment is the key to improve therapeutic efficacy.

In this study, we determined that autologous platelet-rich plasma combined with sodium hyaluronate can improve the clinical efficacy of patients with knee osteoarthritis and inhibit the level of serum inflammatory factors in patients. However, there are still certain limitations in this study. First of all, we did not follow up the patients, so that their long-term efficacy remains unclear in this study. Second, as a single center study, quite limited samples were included. F'inally, since it is a retrospective study, the results of this study may be biased. Therefore, we hope to carry out follow-up in future studies and include more samples to refine our study conclusions.

In summary, the use of intra-articular injection of platelet-rich plasma combined with sodium hyaluronate in the treatment of knee osteoarthritis can significantly reduce knee pain and improve knee function and in vivo inflammatory response.

Disclosure of conflict of interest

None.

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References

[1] Sacitharan PK. Ageing and osteoarthritis. Subcell Biochem 2019; 91: 123-159.

[2] Pereira D, Ramos E and Branco J. Osteoarthritis. Acta Med Port 2015; 28: 99-106.

[3] Michael JW, Schluter-Brust KU and Eysel P. The epidemiology, etiology, diagnosis, and treatment of osteoarthritis of the knee. Dtsch Arztebl Int 2010; 107: 152-162.

[4] Giwnewer U, Rubin G, Orbach H and Rozen N. Treatment for osteoarthritis of the knee. Harefuah 2016; 155: 403-406.

[5] Nagao M, Ishijima M, Kaneko H, Takazawa Y, Ikeda H and Kaneko K. Physical activity for knee osteoarthritis. Clin Calcium 2017; 27: 25-30.

[6] Emmert D, Rasche T, Stieber C, Conrad R and Mucke M. Knee pain - symptoms, diagnosis and therapy of osteoarthritis. MMW Fortschr Med 2018; 160: 58-64.

[7] Tang X, Wang S, Zhan S, Niu J, Tao K, Zhang Y and Lin J. The prevalence of symptomatic knee osteoarthritis in China: results from the China Health and Retirement Longitudinal Study. Arthritis Rheumatol 2016; 68: 648-653.

[8] Kan HS, Chan PK, Chiu KY, Yan CH, Yeung SS, Ng YL, Shiu KW and Ho T. Non-surgical treatment of knee osteoarthritis. Hong Kong Med J 2019; 25: 127-133.

[9] Jang S, Lee K and Ju JH. Recent updates of diagnosis, pathophysiology, and treatment on osteoarthritis of the knee. Int J Mol Sci 2021; 22: 2619.

[10] Richards MM, Maxwell JS, Weng L, Angelos MG and Golzarian J. Intra-articular treatment of knee osteoarthritis: from anti-inflammatories to products of regenerative medicine. Phys Sportsmed 2016; 44: 101-108.

[11] Yaftali NA and Weber K. Corticosteroids and hyaluronic acid injections. Clin Sports Med 2019; 38: 1-15.

[12] Tang JZ, Nie MJ, Zhao JZ, Zhang GC, Zhang Q and Wang B. Platelet-rich plasma versus hyaluronic acid in the treatment of knee osteoarthritis: a meta-analysis. J Orthop Surg Res 2020; 15: 403.

[13] Wu PI, Diaz R and Borg-Stein J. Platelet-rich plasma. Phys Med Rehabil Clin N Am 2016; 27: 825-853.

[14] Everts P, Onishi K, Jayaram P, Lana JF and Mautner K. Platelet-rich plasma: new performance understandings and therapeutic considerations in 2020. Int J Mol Sci 2020; 21: 7794.

[15] Justicz N, Derakhshan A, Chen JX and Lee LN. Platelet-rich plasma for hair restoration. Facial Plast Surg Clin North Am 2020; 28: 181-187.

[16] Xu J, Gou L, Zhang P, Li H and Qiu S. Platelet-rich plasma and regenerative dentistry. Aust Dent J 2020; 65: 131-142.

[17] Zhang Z, Huang C, Jiang Q, Zheng Y, Liu Y, Liu S, Chen Y, Mei Y, Ding C, Chen M, Gu X, Xing D, Gao M, He L, Ye Z, Wu L, Xu J, Yang P, Zhang X, Zhang Y, Chen J, Lin J, Zhao L, Li M, Yang W, Zhou Y, Jiang Q, Chu CQ, Chen Y, Zhang W, Tsai WC, Lei G, He D, Liu W, Fang Y, Wu D, Lin J, Wei CC, Lin HY and Zeng X. Guidelines for the diagnosis and treatment of osteoarthritis in China (2019 edition). Ann Transl Med 2020; 8: 1213.

[18] Sung YT and Wu JS. The Visual Analogue Scale for Rating, Ranking and Paired-Comparison (VAS-RRP): a new technique for psychological measurement. Behav Res Methods 2018; 50: 1694-1715.

[19] Panagopoulos A, Billis E, Floros GR, Stavropoulos T, Kaparounaki E, Moucho M, Paskou A and Tegner Y. Cross-cultural adaptation of the Greek versions of the lysholm knee scoring scale and Tegner activity scale. Cureus 2020; 12: e9372.

[20] Xia B, Di C, Zhang J, Hu S, Jin H and Tong P. Osteoarthritis pathogenesis: a review of molecular mechanisms. Calcif Tissue Int 2014; 95: 495-505.

[21] Cooper C, Rannou F, Richette P, Bruyere O, Al-Daghri N, Altman RD, Brandi ML, Collaud Basset S, Herrero-Beaumont G, Migliore A, Pavelka K, Uebelhart D and Reginster JY. Use of intraarticular hyaluronic acid in the management of knee osteoarthritis in clinical practice. Arthritis Care Res (Hoboken) 2017; 69: 1287-1296.

[22] Billesberger LM, Fisher KM, Qadri YJ and Boortz-Marx RL. Procedural treatments for knee osteoarthritis: a review of current injectable therapies. Pain Res Manag 2020; 2020: 3873098.

[23] Bennell KL, Hunter DJ and Paterson KL. Platelet-rich plasma for the management of hip and knee osteoarthritis. Curr Rheumatol Rep 2017; 19: 24.

[24] Dorio M, Pereira RMR, Luz AGB, Deveza LA, de Oliveira RM and Fuller R. Efficacy of platelet-rich plasma and plasma for symptomatic treatment of knee osteoarthritis: a double-blinded placebo-controlled randomized clinical trial. BMC Musculoskelet Disord 2021; 22: 822.

[25] Di Martino A, Di Matteo B, Papio T, Tentoni F, Selleri F, Cenacchi A, Kon E and Filardo G. Platelet-rich plasma versus hyaluronic acid injections for the treatment of knee osteoarthritis: results at 5 years of a double-blind, randomized controlled trial. Am J Sports Med 2019; 47: 347-354.

[26] Chen Z, Wang C, You D, Zhao S, Zhu Z and Xu M. Platelet-rich plasma versus hyaluronic acid in the treatment of knee osteoarthritis: a

meta-analysis. Medicine (Baltimore) 2020; 99: e19388.
[27] Raeissadat SA, Ghazi Hosseini P, Bahrami MH, Salman Roghani R, Fathi M, Gharooee Ahangar A and Darvish M. The comparison effects of intra-articular injection of Platelet Rich Plasma (PRP), Plasma Rich in Growth Factor (PRGF), Hyaluronic Acid (HA), and ozone in knee osteoarthritis; a one year randomized clinical trial. BMC Musculoskelet Disord 2021; 22: 134.
[28] Cao P, Li Y, Tang Y, Ding C and Hunter DJ. Pharmacotherapy for knee osteoarthritis: current and emerging therapies. Expert Opin Pharmacother 2020; 21: 797-809.
[29] Shi L, Wang K, Yu J, Li M, Men G, Ma G and Wang X. Relationship between magnetic resonance T2-mapping and matrix metalloproteinase 1,3 in knee osteoarthritis. Indian J Orthop 2021; 55: 974-982.
[30] Liao CR, Wang SN, Zhu SY, Wang YQ, Li ZZ, Liu ZY, Jiang WS, Chen JT and Wu Q. Advanced oxidation protein products increase TNF-alpha and IL-1beta expression in chondrocytes via NADPH oxidase 4 and accelerate cartilage degeneration in osteoarthritis progression. Redox Biol 2020; 28: 101306.
[31] Szwedowski D, Szczepanek J, Paczesny L, Zabrzynski J, Gagat M, Mobasheri A and Jeka S. The effect of platelet-rich plasma on the intra-articular microenvironment in knee osteoarthritis. Int J Mol Sci 2021; 22: 5492.
[32] Greene MA and Loeser RF. Aging-related inflammation in osteoarthritis. Osteoarthritis Cartilage 2015; 23: 1966-1971.
[33] Kulkarni K, Karssiens T, Kumar V and Pandit H. Obesity and osteoarthritis. Maturitas 2016; 89: 22-28.
[34] Godziuk K, Prado CM, Woodhouse LJ and Forhan M. The impact of sarcopenic obesity on knee and hip osteoarthritis: a scoping review. BMC Musculoskelet Disord 2018; 19: 271.
[35] Ahmed KM, Said HG, Ramadan EKA, Abd El-Radi M and El-Assal MA. Arabic translation and validation of three knee scores, Lysholm Knee Score (LKS), Oxford Knee Score (OKS), and International Knee Documentation Committee subjective knee form (IKDC). SICOT J 2019; 5: 6.
[36] Dainese P, Wyngaert KV, De Mits S, Wittoek R, Van Ginckel A and Calders P. Association between knee inflammation and knee pain in patients with knee osteoarthritis: a systematic review. Osteoarthritis Cartilage 2022; 30: 516-534.